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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,575	03/27/1999	MARTHA KAREN NEWELL	V00139/70028	3748

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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/277,575	NEWELL, MARTHA KAREN	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,8-13,39,44,143,144,147 and 149* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 4, 8-13, 39, 44, 143, 144, 147 and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional applications 60/082,250, 60/101,580 and 60/094,519.

Claims 1, 2, 5-7, 14-38, 40-43, 45-142, 145, 146 and 148 have been canceled.

Claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 are currently pending and are the subject of examination in the present Office Action.

1. In view of Applicant's amendment filed December 13, 2006 no outstanding ground of rejection is maintained.

2. Further review of the claimed invention has necessitated that the following ground of rejection be re-applied to the claims. This Office Action is made non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 3, 4, 8-13, 39, 44, 143, 144, 147 and 149 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing mitochondrial membrane potential in a tumor cell *in vitro*, does not reasonably provide enablement for decreasing mitochondrial membrane potential in a tumor cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It was previously stated: "The claims, reading upon a treatment for cancer, are broadly drawn to contacting tumor cells with an amount of an MHC class II HLA-DR inducing agent and administering an HLA-DR ligand to the tumor cell for the disclosed purpose of delivering a medicament or lytic agent to the tumor cell. The specification is not enabling for the treatment of cancer in this manner.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

HLA-DR is a family of HLA class II haplotypes that is not specific to a tumor cell but is specific to the human subject being treated. As such, class II HLA-DR molecules of the same haplotype are

expressed on every antigen-presenting cell in that subject's body. Based upon the level of knowledge of the artisan, the artisan would expect that every HLA-DR molecule on every antigen-presenting cell in that subject's body was equally capable of up-regulating expression of HLA-DR and capturing said ligand. Capture would not be limited to the cells of the cancer. Accordingly, rather than inducing a response specifically against/in the cancer cells, the artisan would predict that a more generalized response would be generated in all antigen presenting cells in any part of the body. The claims are not limited to, and the specification does not disclose a mechanism for, specifically targeting the peptide to the HLA-DR-expressing cells of the tumor without allowing normal antigen presenting cells of the subject to also capture and be affected by the ligand binding to HLA-DR.

In view of the nature of the invention, the state of the art, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute."

It was further previously stated: "Applicant's arguments filed August 15, 2005 have been fully considered but they are not persuasive.

Applicant argues that the claimed invention is fully enabled for *in vivo* therapy and that the rejection is merely based on clinical safety issues that are not a test for enablement. Contrary to Applicant's position, the enablement rejection is not based upon clinical safety, but the fact that the invention as claimed cannot target the specific cells to which the agent is supposed to be directed. Applicant attempts to bolster the argument for enablement by pointing out the clinical use of ADRIAMYCIN. ADRIAMYCIN, a trademark for doxorubicin hydrochloride, is an anthracycline antibiotic used for cancer chemotherapy that targets actively dividing cells. Doxorubicin is structurally unrelated to the agents recited in the claim, being composed of an adriamycinone element linked to a daunosamine ring, which intercalates DNA of actively dividing cells, such as rapidly dividing tumor cells. Accordingly, ADRIAMYCIN could be considered preferential in its targeting of tumor cells. The same could not be said for the agents of the instantly claimed invention. ADRIAMYCIN is structurally and functionally distinct from the agents recited in the claim. Merely equating an observed *in vitro* effect of ADRIAMYCIN to an observed *in vitro* effect of the agents recited in claims 3 and 39 does not translate into a comparison of *in vivo* delivery of the agents.

Applicant further argues that the specification teaches "a delivery vehicle such as a liposome to target tissue such as the site of a tumor." However, while claims are to be read in light of the specification, and limitations from the specification are not to be read into the claims. The claims are to be read in their broadest reasonable context."

It was further previously stated: "Applicant argues that the specification is fully enabling for the claimed invention and that the Examiner has failed to make a prima facie case for a lack thereof. Applicant asserts that the Examiner has misunderstood Applicant's previous arguments. The Examiner disagrees with both statements. The claims are drawn to a method of treatment. While, as asserted by Applicant, not all claims are drawn to the treatment of a tumor, all claims are drawn to an in vivo treatment method wherein MHC class II expression is induced or increased upon the cell. The treatment then further calls for attacking the cell expressing MHC class II with an MHC class II ligand in order to "decrease mitochondrial potential" or cause lysis of the target cell. The claimed method is not drawn simply to the upregulation of MHC class II expression on cells which either do or don't constitutively express MHC class II on their surface, rather the method includes a further step of eliminating the MHC class II cells. it has not been questioned by the Examiner as to whether applicant could up-regulate MHC class II expression on the cells, rather the lack of enablement comes into play in regard to the ability to target a desired population of cells for elimination, or "reduction of mitochondrial membrane potential," with a second agent that is an MHC class II ligand. the MHC class II ligand will bind to all MHC class II

expressing cells with equal affinity and reduce mitochondrial membrane potential or lysis of the cells. Irrespective of whether the expression on MHC class II on a given cell is naturally occurring, such as an antigen presenting cell, or induced by Applicant's first step of the claimed method, such as on a tumor cell [claim 39] or a "mammalian cell which is not an antigen presenting cell" [claim 13], the MHC class II haplotype expressed on all cells in the body of the subject being treated will be of the same haplotype. Applicant's method does not cause the expression of a haplotype on target cells that is different than that expressed by antigen presenting cells. Accordingly, Applicant's method will equally lyse or decrease mitochondrial membrane potential on the induced cells and natural antigen presenting cells. the claimed method is not enabled by the specification because Applicant has no way of differentiating between antigen presenting cells and the desired target cells in the second, lysis or decreasing mitochndrial membrane potential, step. Applicant's reliance upon ADRIAMYCIN as the agent that reduces mitochondrial membrane potential as being an example enabling Applicant's broad recitation is not credible. The properties of ADRIAMYCIN were discussed in the previous Office Action. ADRIAMYCIN interchelates DNA in actively dividing cells, such as tumor cells. However, this characteristic does not describe the vast majority of mature antigen presenting cells which express MHC class II. The "class of molecules" Applicant is attempting to represent using ADRIAMYCIN to demonstrate functionality or safety of the class is much broader than just DNA intercalating agents, so it is unclear how ADRIAMYCIN can be considered representative of the class. Applicant refers to the MPEP regarding the applicability of a model to a specific condition. However it is noted that all of Applicant's examples from the specification are in vitro examples carried out in isolated cells. The claimed invention, however, encompasses and recites in vivo treatment of a subject. The specification is not enabling for such an in vivo treatment because there is no evidence that the claimed method would be able to affect the recited target cells of the method in a whole body system context."

Applicant's cumulative arguments have been fully considered but they are not persuasive.

Applicant argues that the claimed invention is enabled because Applicant has provided sufficient evidence from the art that the reagents can be targeted to specific cells. However, this is neither reflected in the claims, nor is there in vivo evidence in the specification that the disclosure is indeed enabling for the delivery. For example, in the liposome citation on page 6 from Applicant's reply filed august 11, 2006, it states that the liposome could be attached to "a monoclonal antibody, sugar, glycolipid, or protein." While a monoclonal antibody could indeed be specific for a specific target cell, it is unclear how a sugar or glycolipid would specifically target a desired cell type versus a normal antigen-presenting cell. In regard to the "protein" recitation, only a protein that interacts with a specific ligand or receptor on the target cell would satisfy the asserted property of direct delivery, however no such provision is made. Claim 11 recites where the inducing agent and the ligand are administered "orally." It is unclear how an oral administration could possibly be construed as being able to deliver the reagents directly to the target cells. For the reasons made of record previously and the reasons stated here, it is maintained that the claimed invention is not enabled. The artisan would not know how to practice the claimed invention and deliver the reagents specifically to the target cells.

Conclusion

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D. RV
Patent Examiner
February 6, 2006

David A Saunders
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PRIMARY EXAMINER